



## Post Approval Study

### **A Multi Center, Post Approval Study Providing Continued Evaluation and Follow-up on Patients Who Received a HeartWare® Ventricular Assist System During IDE Trials for the Treatment of Advanced Heart Failure**

<b>Investigational Product:</b>	<b>HeartWare® Ventricular Assist System</b>
<b>Post Approval Study Number:</b>	<b>HW-PAS-03</b>
<b>Date:</b>	<b>04 September, 2013</b>

*This post approval study contains confidential information for use by investigators and their designated representatives participating in this clinical investigation. It should be held confidential and maintained in a secure location. It should not be copied or made available for review by any person or firm without the prior written consent of HeartWare, Inc.*

## 1.0 Administrative Information

### 1.1 Contacts

#### Medical, Clinical and Operational Support

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### 1.2 Administrative Information

Post Approval Study Number: HW-PAS-03  
Revision Number: 3.0  
Protocol Date: 04 September 2013  
Product: HeartWare® Ventricular Assist System (VAS)

### 1.3 Amendment History:

Date	Amendment Number	Amendment Type
20 September 2012	1.0	Original Protocol
31 May 2013	2.0	Revised Submission
04 September 2013	3.0	Revised Submission

## 1.4 Sponsor Approval

### Representatives of HeartWare

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this Post Approval Study and all applicable local laws and regulations, including, without limitation, data privacy laws and regulations.

### SIGNATURES

**Sponsor  
Signatory:**

**Signature:**

**Date:**

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CONFIDENTIAL

## 1.5 Investigator agreement

I will provide copies of the Post Approval Study and all pertinent information to all individuals responsible to me who assist in the conduct of the study. I will discuss this material with them to ensure they are fully informed regarding the investigational products and the conduct of the study.

I will use only the informed consent form approved by the sponsor and the Institutional Review Board/Independent Ethics Committee (IRB) or its representative.

I also understand that this study will not be initiated without approval of the appropriate Institutional Review Committee and that all administrative requirements of the governing body of the institution will be complied with fully.

I will obtain written informed consent from all participating subjects in accordance with requirements as specified in ICH Guideline for Good Clinical Practice; Section 48 (ICH GCP).

I also agree to report all information or data in accordance with the Post Approval Study and, in particular, I agree to report without unjustified delay, all Serious Adverse Events (SAEs) and Device Deficiencies (DDs) that could have led to a reportable event.

I further agree that HeartWare and/or designee will have access to any original source documents from which electronic case report form (eCRF) information may have been generated.

I also agree to have control over all clinical supplies provided by HeartWare and/or designee and collect, account and handle all clinical specimens in accordance with the Post Approval Study protocol.

I further agree not to originate or use the name of HeartWare Inc. and/or HeartWare® Ventricular Assist System, or any of its employees, in any publicity, news release or other public announcement, written or oral, whether to the public, press or otherwise, relating to this Post Approval Study, to any amendment hereto, or to the performance hereunder, without the prior written consent of HeartWare Inc.

I herewith declare that I agree with the Post Approval Study described in detail in this document and agree to conduct the Post Approval Study in accordance with this document and in compliance with Good Clinical Practice and all applicable regulatory requirements.


Investigator Name (print) \_\_\_\_\_

Investigator Signature \_\_\_\_\_ Date \_\_\_\_\_

Name of Facility \_\_\_\_\_

Location of Facility (City) \_\_\_\_\_

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## 2.0 STUDY SUMMARY

<b>Name of Sponsor(s):</b> HeartWare Inc.	
<b>Device:</b> HeartWare® VAS is an implantable centrifugal blood pump, with the following major components: Implantable Blood Pump with Conduits, Controller, Monitor, Batteries, Battery Charger and Accessories	
<b>Title of Post Approval Study:</b> A Multi Center, Post Approval Study Providing Continued Evaluation and Follow-up on Patients Who Received a HeartWare® Ventricular Assist System During IDE Trials for the Treatment of Advanced Heart Failure.	
<b>Post Approval Study Number:</b> HW-PAS-03	
<b>Post Approval Study Design:</b> Open label, observational, follow-on study.	
<b>Endpoints:</b> Endpoints that will be assessed include: <ul style="list-style-type: none"> <li>• Overall survival</li> <li>• Re-hospitalizations</li> <li>• Quality of Life improvement, as measured by KCCQ and EuroQol EQ-5D</li> <li>• Incidence of INTERMACS® adverse events and unanticipated adverse device effects.</li> <li>• Incidence of all device failures and device malfunctions</li> <li>• Functional status improvement, as measured by NYHA and 6-minute walk</li> </ul>	
<b>Intended Use:</b> The HeartWare® Ventricular Assist System (VAS) is intended for use as a bridge to cardiac transplantation in patients who are at risk of death from refractory end-stage left ventricular heart failure. The HeartWare® VAS is designed for in-hospital and out-of-hospital settings, including transportation via fixed wing aircraft or helicopter.	
<b>Number of Subjects:</b> Subjects from IDE G070199 that meet the criteria will be enrolled.	<b>Number of Sites:</b> Up to 25
<b>Period of Evaluation:</b> All patients will have an enrollment visit and then be followed at 6 month intervals until 5 years post implant of the original HeartWare® device.  Patients who are explanted for transplant or recovery will be followed to 6 months post explant at which point their participation in the trial will be considered complete. This visit will record patient status only.	
<b>Main Criteria for Inclusion:</b> <ol style="list-style-type: none"> <li>1. The patient has participated in a prior HeartWare trial under IDE G070199.</li> <li>2. The patient was implanted with the HeartWare® VAS and was an active patient in the prior trial.</li> <li>3. The patient has signed informed consent for participation in the study.</li> </ol>	
<b>Main Criteria for Exclusion:</b> <ol style="list-style-type: none"> <li>1. The patient is unwilling or unable to comply with trial requirements.</li> <li>2. The patient did not sign the informed consent.</li> </ol>	
<b>Main Criteria for Evaluation and Analyses:</b> Endpoints that will be assessed include; overall survival on device, final patient status, re-hospitalizations, INTERMACS® adverse events, Quality of Life measures, functional status. Safety measures will include the frequency and rates of adverse events, overall and for each specific event, which will be collected throughout HeartWare® VAS support	
<b>Sample Size Justification and Statistical Considerations:</b> Not Applicable as this is a follow-up study only and does not involve the screening and implant of new patients.	



## 3.0 Study Reference Information

### 3.1 List of Standard Abbreviations

Abbreviation	Definition
ACE	Angiotensin-converting enzyme
AE	Adverse Event
ALT	Alanine aminotransferase
ARB	Angiotensin Receptor Blocker
AST	Aspartate aminotransferase
BP	Blood Pressure
BSA	Body Surface Area (m <sup>2</sup> )
BTT	Bridge to Transplantation
BUN	Blood Urea Nitrogen
CFR	Code of Federal Regulations
CK	Creatine Kinase
CNS	Central Nervous System
CRF	Case Report Form
CRO	Clinical Research Organization
CSS	Clinical Summary Score of KCCQ
CVA	Cerebral Vascular Accident (stroke)
CVP	Central Venous Pressure
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
EQ-5D	EuroQol Questionnaire (Health Status tool)
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
HF	Heart Failure
Hgb	Hemoglobin
ICF	Informed Consent Form
IDE	Investigational Device Exemption
IFU	Instructions for Use
IRB	Institutional Review Board
ICH	International Conference on Harmonisation
INR	International Normalized Ratio
INTERMACS®	InterAgency Registry for Mechanical Assisted Circulatory Support
ISHLT	International Society for Heart & Lung Transplantation
KCCQ	Kansas City Cardiomyopathy Questionnaire ( tool)
LED	Light Emitting Diode
LV	Left Ventricle

Abbreviation	Definition
LVAD	Left Ventricular Assist Device
LVEF	Left Ventricular Ejection Fraction
Mb	Myoglobin
MCS	Mechanical Circulatory Support
MCSD	Mechanical Circulatory Support Device
MedDRA	Medical Dictionary for Regulatory Activities
mL	milliliter
MI	Myocardial Infarction
MRS	Modified Rankin Scale
NIH	National Institutes of Health
NIHSS	National Institutes of Health Stroke Scale
NYHA	New York Heart Association (heart failure classification)
PAS	Post Approval Study
PI	Principal Investigator
Pt / Pts	Patient / Patients
PMA	Premarket Approval
PTT	Partial Thromboplastin Time (activated = aPTT)
PVAD	Paracorporeal Ventricular Assist Device
PVR	Pulmonary Vascular Resistance
QoL	Quality of Life
RAP	Right Arterial Pressure
RGA	Returned Goods Authorization
RVAD	Right Ventricular Assist Device
RVEF	Right Ventricular Ejection Fraction
SAE	Serious Adverse Event
SD	Standard Deviation
SE	Standard Error
TE	Thromboembolic Event
TIA	Transient Ischemic Attack
TX	Transplant
UADE	Unanticipated Adverse Device Effect
UNOS	United Network for Organ Sharing
UCL	Upper Confidence Limit
VAD	Ventricular Assist Device
VAS	Ventricular Assist System
WBC	White Blood Cell

## 4.0 INTRODUCTION

### 4.1 Background and Rationale

Heart Failure (HF) is a complex clinical syndrome caused by structural, metabolic and neurohormonal disorders that impair cardiovascular function, and is one of the leading causes of death in the developed world.

The worldwide prevalence of heart failure in adults is estimated to be 2-6%, with a higher prevalence in industrialized nations. Each year in the US, 670,000 new cases are identified<sup>1</sup> and of the prevalent cases, 1 million are end-stage HF (NYHA class IV). There are approximately 5.7 million cases diagnosed in the United States and up to 14 million cases in the European Union<sup>2</sup>. Advanced HF is associated with significant morbidity and disabling symptoms at rest. The one year mortality rate in patients newly diagnosed with NYHA class IV HF is approximately 25%<sup>3</sup>. Improvements in treatment and survival as well as expansion of the aging population have contributed to the rising incidence and prevalence of the disease.

Cardiac transplantation is currently the most effective therapy for advanced heart failure. However, the lack of available donor organs restricts the use of heart transplantation to fewer than 2500 patients per year in the United States. In 2009, 2211 heart transplants were performed at 127 heart transplant centers in the United States (United Network for Organ Sharing website accessed December 15, 2011). Currently there are 3100 patients on the UNOS heart transplant list, with an average waiting time of approximately 6 months<sup>4</sup>.

This Post Approval Study (PAS) is a study to provide continued and consistent follow-up on patients who have participated in prior IDE trials of HeartWare devices. Eligible patients include those who have reached the primary endpoint or outcome of that trial and entered longer term follow-up, as well as, those who have not yet achieved the primary endpoint or outcome at the time of PMA approval.

### 4.2 HeartWare® VAS

A full description of the HeartWare® VAS is included in the Instructions for Use (IFU) for the approved indications.

Ventricular Assist Devices are options for advanced HF patients that sustain life, improve general medical condition and enhance quality of life as they provide a bridge to cardiac transplantation or, in some patients, an alternative permanent therapy. Approximately 32% of the patients who receive heart transplants are bridged with ventricular assist devices (ISHLT 2011 data<sup>4</sup>). The use of permanent LVADs as an alternative to transplantation (Destination Therapy) has also proven to be more effective than medical therapy.<sup>5</sup>

The HeartWare® VAS was designed to assist a failing left ventricle. The HeartWare® VAS utilizes a blood pump, the HVAD® Pump or simply HVAD, which is a continuous flow, centrifugal device with a non-contacting rotating impeller and dual motor stators for compact size and increased fault tolerance. The impeller is suspended by a combination of passive magnetic and hydrodynamic forces. The inflow cannula is an integrated component permanently

affixed to the pump and is attached to the left ventricular apex through a c-clamp type sewing ring. Blood is pumped from the left ventricle into the ascending aorta via a 10mm gel impregnated polyester conduit that can be adjusted to fit patient size and is protected from kinking or compression by a strain relief. This design facilitates surgical implantation entirely within the pericardial space avoiding the necessity for an abdominal pump pocket and potentially reducing perioperative risks such as bleeding and infections. While the HeartWare® VAS is small (160g), it can deliver up to 10 liters/minute of blood flow.

A 4.2 mm diameter percutaneous driveline connects the pump to an external controller. The controller, powered by two batteries or by one battery and electricity from the wall or car outlet, regulates pump function and provides digital messages, alarms and LED light patterns that alert patients to pump parameters that are outside pre-set limits or warn of malfunctions in the system. A separate monitor is used to display system performance and to change controller operating parameters. A battery charger is also included.

### **4.3 Previous Patient and Trial Experience**

#### **4.3.1 CE Mark Trial**

The initial clinical experience with the HeartWare® VAS was a 50 subject BTT trial conducted at 5 centers in Australia, Austria, Germany and the United Kingdom. The first 25 subjects were enrolled between March 2006 and December 2007 and the results were submitted for regulatory approval in the EU. CE Mark was received on January 29, 2009. The trial was continued to enroll another 25 patients for a total of fifty (50) patients, with the last patient enrolled in December 2008.

The primary endpoint of survival to 180 days was successfully reached by 90% (45/50) of the patients.

As of January 18, 2012, 29 of the 50 subjects were transplanted, four were weaned from the HeartWare® VAS due to myocardial recovery, 11 died while on support, and 6 subjects remain on support. All 6 subjects currently supported by HeartWare® VAS have been on the device for more than 3 years, with 2 patients greater than 4 years.

#### **4.3.2 US Bridge to Transplant Trial (ADVANCE)**

The HW003 Evaluation of the HeartWare® VAS for the Treatment of Advanced Heart Failure Trial, or ADVANCE, was a multi-center, prospective trial that used an external contemporaneous control group from the NIH sponsored Inter-Agency Registry for Mechanical Assisted Circulatory Support (INTERMACS®) to compare the efficacy of HeartWare® VAS with commercially approved LVADs. The INTERMACS® control subjects were not homogeneous with respect to the type of left ventricular assist device, although more than 90% of the subjects received the HeartMate II LVAD (Thoratec Corporation) which is the only approved continuous flow LVAD in the United States. In both the HeartWare® VAS and INTERMACS® registry control group, subjects were followed to death, device explant, cardiac transplantation or survival to Day 180.

In ADVANCE there were 160 subjects enrolled at 30 sites. Of the 160 subjects, 17 were screen failures and 143 subjects were implanted with the HeartWare® VAS. Three of these 143 patients were implanted under emergency use treatment. Of the remaining 140 patients implanted, 3 patients were found to have protocol violations which were pre-specified in the statistical analysis plan (SAP) as major violations. As a result, there were 137 subjects in the “per protocol” population and 140 subjects in the “safety” population. The first subject was implanted on August 18, 2008 and the 180 day follow up for the last subject enrolled and implanted was completed August 23, 2010.

*The primary endpoint for the trial was defined as alive on the originally implanted device (HeartWare® VAS or LVAD in the registry control group), transplanted or explanted for recovery at the 180 day time point, all of which collectively constituted “success.”*

Secondary efficacy measures include overall survival, quality of life improvement, as measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ) and EuroQol EQ-5D™ - (EQ-5D) and functional status improvement.

Secondary efficacy measures were based upon change from baseline in the HeartWare® VAS treatment group since registry data were not specified for comparison in the protocol.

Safety endpoints consisted of the incidence of INTERMACS®-defined events, serious adverse events (SAE), including neurocognitive changes, unanticipated adverse device effects (UADE); and device failures and malfunctions. Events were classified and presented according to both the INTERMACS®-defined adverse event categories and MedDRA coded categories. Adverse events from the INTERMACS® control group were not pre-specified to be available for comparison.

The pre-specified primary endpoint analysis was a comparison of success rates using a non-inferiority margin of 15%.

In the HeartWare® VAS group the success rate in the ITT / Safety Population at 180 days was 90.7% (127/140) and in the Per Protocol population 92.0% (126/137). The success for both Safety and Per Protocol populations in the Control group was 90.1% (448/497).

The Primary analysis found that the 95% one-sided upper confidence limit (UCL) on the difference in success rates between HeartWare® VAS group and controls was 4.5% for the Safety population and 0.9% for the Per Protocol population. Each of these limits was less than the 15% non-inferiority margin ( $p < 0.0001$ ).

#### 4.4 Indication for Use

The HeartWare® VAS is intended for use as a bridge to cardiac transplantation in patients who are at risk of death from refractory end-stage left ventricular heart failure. The HeartWare® VAS is designed for in-hospital and out-of-hospital settings, including transportation via fixed wing aircraft or helicopter.

The HeartWare® VAS is contraindicated in patients who cannot tolerate anticoagulation therapy.

#### 5.0 Study Objectives and Endpoint Measures (Endpoints)

The purpose of this multi-center, follow-up trial is to continue the evaluation of the safety and effectiveness of the HeartWare® VAS in patients who have been implanted with the HeartWare® VAS in the course of a prior HeartWare Trial under IDE G070199.

Endpoints that will be assessed include:

- Overall survival on device
- Final patient status
- Re-hospitalizations
- INTERMACS® adverse events
- Quality of Life measures
- Functional Status

Safety measures will include the frequency and rates of adverse events, overall and for each specific event, which will be collected throughout HeartWare® VAS support.

## 6.0 Study Design

No new patients are being screened or implanted with the HeartWare® VAS for this trial; it is a follow-up trial only.

Patients will be approached to participate in this PAS after the HeartWare® VAS receives PMA approval for the indicated use as a bridge to cardiac transplantation.

Patients who participated in a prior trial under IDE G070199 will be approached for this PAS as follows:

- Patients who are on continued HeartWare® VAS support, (original or exchange device)
- Patients who have been explanted for transplant or recovery and have not yet completed 6 months of follow-up

Patients who participated in prior trials under IDE G070199 who will not be approached to participate in this follow-up study include:

- Patients who have been explanted for transplant or recovery and have completed at least 6 months of follow-up (documented in the prior IDE trial).
- Patients who have had their HeartWare® VAS exchanged for another FDA approved VAD (e.g. HMII®)

All patients will have an enrollment visit and then be followed at 6 month intervals until 5 years post implant of the original HeartWare® VAS.

Patients who are explanted for transplant or recovery will be followed to 6 months post explant at which point their participation in the trial will be considered complete. This visit will record patient status only.

### 6.1 Number of Clinical Sites

This follow-up trial will be conducted at up to the 25 sites who enrolled and implanted patients with the HeartWare® VAS under IDE G070199, and who have a patient active under that IDE at the time of approval.

## 6.2 Patient Population

The patient population consists of patients who were at risk of death from refractory, advanced heart failure and implanted with a HeartWare® VAS under IDE G070199.

Patients must have participated as a study patient in a prior HeartWare trial under IDE G070199, and been implanted with the HeartWare® VAS. The following inclusion and exclusion criteria must then be applied:

### 6.2.1 Inclusion Criteria

1. The patient has participated in a prior HeartWare trial under IDE G070199.
2. The patient was implanted with the HeartWare® VAS and was an active patient in the prior trial.
3. The patient has signed informed consent for participation in the study.

### 6.2.2 Exclusion Criteria

1. The patient is unwilling or unable to comply with trial requirements.
2. The patient did not sign the informed consent.

## 6.3 Criteria for Discontinuation or Withdrawal of a Patient

The primary reason for discontinuation or withdrawal of the patient from the study should be noted using the following categories.

1. Lost to follow-up. The patient did not return to the clinic and attempts to contact the patient were unsuccessful. Attempts to contact the patient must be documented.
2. Voluntary withdrawal. The patient wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF. NOTE: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded).
3. Study termination. The sponsor, Institutional Review Board (IRB), or regulatory agency terminates the study.
4. Other. NOTE: The specific reasons, or, if a patient refuses to give a reason, should be recorded accordingly in the eCRF.

## 6.4 Procedure for Discontinuation or Withdrawal of a Subject

A patient may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary reason for termination must be recorded in the eCRF. Efforts should be made to perform all procedures scheduled for the Year 5 visit.



## 7.0 Sample Size

Sample size calculations are not applicable for this observational follow-on trial.

## 8.0 Study Endpoints

This is a follow-on study and endpoints are observational only.

### 8.1 Observational endpoints

Observational endpoints for this trial include:

- Overall survival on device
- Final patient status
- Re-hospitalizations
- INTERMACS® adverse events
- Quality of Life measures
- Functional Status

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

## 9.0 Study Course and Visits

The following sections describe the procedures to be completed throughout the conduct of the study. The Schedule of Study Procedures is described in this section [REDACTED]. Every attempt should be made to perform evaluations at the designated time points. For visits conducted every 6 months post implant, there is a window of ± 60days.

Post IRB Approval of this study, patients will be consented to participate at their next visit for the IDE trial, which will be considered their final visit. At that visit their participation in the IDE trial will be halted and they will be provided information about this PAS, and if they give written informed consent to participate they will be considered enrolled in this PAS.

### 9.1 Informed Consent Procedure

Before enrolling the patient in the trial, i.e., any trial-related procedure is performed; written ICF must be obtained. Each potential participant shall be informed of the aim of the trial and what participation entails. They shall be supplied with an Information Sheet summarizing the details of the trial. Ample time should be given to the subjects to consider their participation. Agreement to participate in the trial is to be confirmed by the patient and the Principal Investigator (or authorized designee) signing and dating the consent form. Documentation of this procedure is required in the medical record.

### 9.2 Visits and Assessments

Assessments will be conducted at enrollment and at follow-up visits. Patients active on device will have follow-up visits every 6 months until outcome or 5 years post implant of the original device. There will be additional assessments if patients reach an outcome i.e., are re-hospitalized, have the device explanted or replaced, and in the event of a patient death.

Study visits and assessment are described as follows:

#### 9.2.1 Enrollment Visit for Patients Active on Device

The following procedures will be performed:

- Obtain signed and dated written ICF
- Inclusion/Exclusion
- Date of Assessment
- Record Demographics
- Measure Hemodynamic parameters
- Collect blood samples for laboratory testing
- Record LVAD Parameters
- Perform NYHA Classification
- Perform 6- Minute Walk Test
- Record patient status
- Patient device strategy

- NIH Stroke Scale/Modified Rankin Scale
- Collect Neurocognitive function data
- Collect Kansas City Cardiomyopathy Questionnaire
- Collect Quality of life questionnaire (EuroQol EQ-5D-5L)
- Record concomitant medication taken by the patient
- Document adverse events reported from date of signature of the ICF including ongoing adverse events from the premarket trial

If an enrollment visit occurs within the protocol allowed window for a 6 month follow-up visit, then the enrollment visit takes the place of that 6 month follow-up visit. The patient then resumes their follow up schedule based upon their original implant date.

Additionally the patient identifier from the prior trial and the trial ID will be captured.

### **9.2.2 Enrollment Visit for Patients not on Device**

- For patients who have been explanted for transplant or recovery in the prior IDE trial, and have not completed 6 months post explant follow up the following procedures will be performed: Obtain signed and dated written ICF
- Date of Assessment
- Record patient status

Additionally the patient identifier from the prior trial and the trial ID will be captured.

### **9.2.3 6 Month Follow up Assessments for Patients Active on Device**

The following procedures will be performed:

- Date of Assessment
- Measure Hemodynamic parameters
- Collect blood samples for laboratory testing
- Record LVAD Parameters
- Perform NYHA Classification
- Perform 6- Minute Walk Test
- Record patient status
- Patient device strategy
- NIH Stroke Score/Modified Rankin Scale
- Collect Neurocognitive function data
- Collect Kansas City Cardiomyopathy Questionnaire
- Collect Quality of life questionnaire (EuroQol EQ-5D-5L)
- Record concomitant medication taken by the subject
- Document adverse events reported

#### **9.2.4 6 Month Follow-up Assessments for Patients not on Device**

For patients who have been explanted for transplant or recovery (or device turned off in lieu of surgical explant), the following data will be collected at 6 months post explant only:

- Date of Assessment
- Record patient status

After the 6 month follow up visit the patient's participation in the study will be complete.

#### **9.2.5 6 Month Follow-up Assessments for Patients who Exchange for Another Type of LVAD**

For patients who have had their HeartWare® VAS exchanged to another FDA approved VAD (e.g. HMII®) the following data will be collected at 6 months post exchange only:

- Date of Assessment
- Record patient status

After the 6 month post exchange follow up visit the patient's participation in the study will be complete.

#### **9.2.6 Re-Hospitalizations**

Information on re-hospitalizations post initial discharge will be collected. This includes date and reason for readmission, treatment and date of discharge.

#### **9.2.7 Device Explant**

In the event that the HeartWare® VAS is explanted (i.e. death, transplant, recovery, device exchange) observations should be documented in the eCRF.

The rationale for explant of the HeartWare® VAS will be recorded on the eCRF.

Reasons may include:

- Heart Recovery
- Heart Transplantation
- HeartWare® VAS Exchange
- Mortality or
- Alternative Device Implant

At explant, the HeartWare® VAS and the incision sites should be inspected for:

- Pump condition prior to explant,
- Pericardial or pump pocket condition,
- Sewing Ring condition,
- Outflow Conduit condition and position,
- Driveline status,

- Blood pump housing condition.

Any identified unusual findings are to be reported on the eCRF.

The HeartWare® VAS should NOT be disassembled by the center. See the IFU for the approved Indication for the HeartWare® VAS Explant procedure.

***The HeartWare® VAS components shall be returned to HeartWare in all cases in which the device/component is suspected to have malfunctioned or it is replaced for any reason as the result of an adverse event.***

For HeartWare® VAS devices that need to be returned, HeartWare will provide an Explant Kit that is designed for transportation of used health care products. Packaging instructions will be included in each Explant Kit.

An Explant Kit is available by contacting HeartWare Customer Support at 1-(305)-364-2500 or email [cs@heartwareinc.com](mailto:cs@heartwareinc.com).

### 9.2.8 Outcomes

Information on the type of outcome (transplant, explant, death) will include transplant date, reason for explant, and cause of death. Patients who have been transplanted or have been explanted will be followed until 6 months post outcome.

## 10.0 Procedures

The following are a description of the procedures that will be conducted during patient visits.

### 10.1 Demography

The standard demographics of age, date of birth, gender, height, weight, race, and patient-described ethnicity will be recorded during enrollment visit only.

### 10.2 General Hemodynamics

General hemodynamics to be collected are:

- Heart rate
- Blood pressure (Systolic/Diastolic and Mean)

### 10.3 Documentation of Concomitant Medications

All cardiac medications including inotropes, nesiritide, angiotensin receptor blockers, amiodarones, beta blockers, ACE inhibitors, aldosterone antagonists, loop diuretics, anticoagulants, antiplatelet therapy drugs and nitric oxide will be captured at Enrollment and every 6 months until year 5 post-implant or study discontinuation (whichever comes first).

Any Concomitant Medications taken prior, up to onset and to treat an Adverse Event will be collected at the time of each event, including any specific medications pertaining to the anticoagulation guidelines for thromboembolism, stroke and / or VAD thrombosis.

### 10.4 Safety Laboratory Investigations

Laboratory samples will be taken for all patients active on device at enrollment and at every follow-up visit (every 6 months until year 5 post-implant or study discontinuation whichever comes first).

The laboratory variables that will be determined are listed below:

#### Hematology

White Blood Cell Count	Platelet
Hemoglobin	INR

#### Biochemistry

Sodium	LDH
Potassium	Total Bilirubin
Blood Urea Nitrogen	Bilirubin direct and Indirect
Creatinine	Albumin
SGPT/ALT	Cholesterol
SGOT/AST	

### 10.5 HeartWare® Pump Parameters

LVAD parameters of Flow (L/min), Speed (RPM) and Power (Watts), along with documentation of suction detection status and status of alarm reporting will be recorded at enrollment and every 6 months until year 5 post-implant or study discontinuation (whichever comes first).

### 10.6 Exercise Function (Six Minute Walk)

Assessment of exercise function consists of a six minute walk test and will be completed at enrollment and every 6 months until year 5 post-implant or study discontinuation (whichever comes first).

All efforts should be made to perform the 6 minute walk test for any patient able to walk more than a few steps. If the patient is unable or unwilling to perform the six-minute walk test, the result will be recorded as not done. If the six minute walk test was not completed the reason will be recorded. [REDACTED]

### 10.7 NYHA classification

[REDACTED] Determination of NYHA classification will be performed by an independent assessor (defined as a physician or qualified physician assistant (PA), registered nurse (RN) or nurse practitioner (NP) not directly involved with this clinical trial). The name of the assessor will be recorded on the Case Report Form and in the medical files.

NYHA will be captured for all patients at enrollment and every follow up visit (every 6 months until year 5 post-implant or study discontinuation, whichever comes first)

### 10.8 NIH Stroke Scale/ Modified Rankin Scale

For patients active on device, a trained individual will obtain the National Institutes of Health Stroke Scale (NIHSS) and Modified Rankin Scale (MRS), [REDACTED] at the enrollment visit and every follow up visit (every 6 months until year 5 post-implant or study discontinuation, whichever comes first)

In addition, the NIH Stroke Scale and MRS are required in the event of a stroke. After a stroke, follow-up NIH Stroke Scale and MRS are captured at each 6 month follow up visit.

## 10.9 Patient Device Strategy

Current Device Strategy determined in conjunction with the heart failure cardiologist and surgeon at the time of the implant should be re-visited and recorded at enrollment and every follow up visit (every 6 months until year 5 post-implant or study discontinuation, whichever comes first)

The strategy should be selected as:

- Bridge to recovery
- Bridge to transplant
- Possible bridge to transplant
- Destination therapy

If the patient device strategy has changed from the prior visit, the reason for the change in device strategy will be recorded in the eCRF.

## 10.10 Quality of life Questionnaire (EuroQol EQ-5D-5L)

The EQ-5D-5L [REDACTED]; an assessment of general well-being will be utilized. Assessment will be performed for patients at enrollment and every follow up visit (every 6 months until year 5 post-implant or study discontinuation, whichever comes first)

## 10.11 Kansas City Cardiomyopathy Questionnaire (KCCQ)

This study will use the KCCQ [REDACTED], a disease specific 23-item, self-administered instrument that quantifies physical function, symptoms (frequency, severity and recent change), social function, self-efficacy and knowledge and quality of life. Patients will complete the KCCQ at enrollment and every follow up visit (every 6 months until year 5 post-implant or study discontinuation, whichever comes first)

## 10.12 Neurocognitive Testing

Neurocognitive function data [REDACTED] will be measured by the Trial Making Neurocognitive Test, Part B at enrollment and every follow up visit (every 6 months until year 5 post-implant or study discontinuation, whichever comes first). This test of general cognitive function also specifically assesses working memory, visual processing, visuospatial skills, selective and divided attention and psychomotor coordination for the Neurocognitive Function Test)



## 11.0 Adverse Events

Adverse events collected will be captured and categorized according to NIH funded INTERMACS® registry defined adverse events, and this will also include any serious and/or non-serious AEs not meeting the INTERMACS® definitions that are noted to be clinically relevant by the PI. These will be recorded on the appropriate eCRF.

Adverse events will be collected throughout the subject's participation in this follow-up trial while on device support, and the subject instructed to report any event to the investigator when and /or as it occurs.

In the event of an explant for transplant or recovery, adverse events will be collected until the induction of anesthesia for explant.

In the event the device is turned off in lieu of surgical explant, adverse events will be collected until the time the device is turned off.

In the event of an explant for an exchange for another HeartWare® VAS, the subject will remain in the study post device exchange and adverse events will be collected throughout the subject's participation in this follow-up trial.

In the event of an explant for exchange for another FDA approved VAD (e.g. HMII®), adverse events will be collected until the induction of anesthesia for exchange.

### 11.1 INTERMACS®-defined adverse events

These INTERMACS®-defined adverse events include:

- Major infection
- Neurological dysfunction
- Major bleeding
- Device malfunction

And also

- Cardiac arrhythmia
- Hemolysis
- Hepatic dysfunction
- Hypertension
- Myocardial infarction
- Pericardial fluid collection
- Psychiatric episode
- Renal dysfunction
- Respiratory failure
- Right heart failure
- Arterial non-CNS thromboembolism
- Venous thromboembolism
- Wound dehiscence
- Other adverse events

The above referenced events will be coded as the INTERMACS® defined adverse event term.

Events that fall into the category of INTERMACS® “Other” will be reviewed, classified, and coded according the Medical Dictionary for Regulatory Activities (MedDRA).

## 11.2 Device Malfunctions

Information on device malfunctions reported by Investigators or reported directly to HeartWare will be reviewed and reported to FDA as required by the Medical Device Reporting regulations (21 CFR 803).

HeartWare will conduct analyses on devices and device components returned to HeartWare to confirm device malfunctions.

## 11.3 Definition of Adverse Event (AE)

Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the medical device. This includes events related to the procedures involved in this Post Approval Study. For users or other persons this is restricted to events related to the medical device.

## 11.4 Definition of Serious Adverse Event (SAE)

Serious Adverse events are those that:

- Result in death
- Are life-threatening
- Require intervention to prevent permanent impairment/damage
- Result in persistent or significant disability/ incapacity
- Require hospitalization or unduly prolongation of existing hospitalization
- Result in congenital anomaly

## 11.5 Unanticipated Adverse Device Effects

Any serious adverse effects on health or safety, or any life-threatening problem caused by the LVAD that was not previously identified in nature, severity or degree of incidence in the protocol or any other serious problem associated with the device that relates to the rights, safety or welfare of the subject.

## 11.6 Anticipated Adverse Events

Adverse events that may be anticipated during the implant of the HeartWare® VAS, or are associated with the continued use and support on the device include the following:

- |                                    |                                |
|------------------------------------|--------------------------------|
| • Air Embolism                     | • Aortic Insufficiency         |
| • Bleeding, Perioperative or Late  | • Cardiac Arrhythmias          |
| • Death                            | • Device Malfunction           |
| • Device Thrombosis                | • Driveline Infection          |
| • Driveline Perforation            | • Driveline Wire Damage        |
| • Erosions and other Tissue Damage | • GI Bleeding/AV malformations |
| • Hemolysis                        | • Hepatic Dysfunction          |

- Hypertension
- Local Infection
- Myocardial Infarction
- Organ Damage During Driveline Tunneling
- Peripheral Thromboembolism
- Pleural effusion
- Renal Dysfunction
- Respiratory Dysfunction
- Sensitivity to Aspirin
- Stroke
- Wound Dehiscence
- Interference with/from Other Devices
- Multi-organ Failure
- Neurologic Dysfunction
- Pericardial Effusion/Tamponade
- Platelet Dysfunction
- Psychiatric Episodes
- Re-operation
- Right Ventricular Failure
- Sepsis
- Worsening Heart Failure

## 11.7 Adverse Event Reporting Requirements

Adverse events will be reported using the NIH funded INTEMACS registry definitions

All adverse events will be recorded from the time of signature of Informed Consent until a subjects participation in the trial is considered complete, or at the time of induction of anesthesia if the device is explanted for recovery or transplantation or exchange to another FDA approved VAD (e.g. HMII®), or at the time the HeartWare® VAS is turned off in lieu of surgical explant.

It is the responsibility of the investigators to inform their IRB of adverse events as required by their local IRB procedures.

### 11.7.1 UADE Reporting

HeartWare's evaluation of the UADE must be reported to the FDA through Medical Device Reports (MDRs). UADE's must be reported to all reviewing IRBs, and participating investigators within 10 working days of knowledge of the event by HeartWare.

## **12.0 Device and Patient Management**

In the case of device replacement during the study for patient management please refer to the approved IFU for the HeartWare® VAS.

### **12.1 Infection Control**

It is recommended that centers follow the Infection Control Guidelines in the IFU of the approved indication of the HeartWare® VAS.

### **12.2 Anticoagulation Guidelines**

It is recommended that centers follow the Anticoagulation Guidelines in the IFU of the approved indication of the HeartWare® VAS.

### **12.3 Return or Readmission to Hospital**

Patients must return and/or be readmitted to the hospital for any of the following conditions:

- The occurrence of any HeartWare® VAS malfunctions or alarm conditions that cannot be immediately diagnosed and corrected in the field, the Guidelines are to be followed as listed in in the IFU of the approved indication.
- Medical emergency (e.g., cardiac arrest, HeartWare® VAS stops, loss of consciousness).
- Medical conditions (e.g., new onset infection, neurological complication) or other conditions as determined by the physician.
- Loss of power to the residence that is expected to last a period of time equivalent to or in excess of one-half the available battery support time.

### 13.0 Statistical Analysis

Data collected in this study will be reported using summary tables and subject data listings.

Descriptive statistics (n, mean, median, standard deviation, minimum and maximum) will be considered for continuous variables; frequencies and percentages will be considered for categorical variables.

Baseline and demographic data will be summarized [REDACTED]

For outcomes such as death, [REDACTED] a Kaplan-Meier (time to event) analysis will be used. [REDACTED]

For QOL, Neurocognitive and Functional assessments, analyses may involve a comparison to baseline. [REDACTED]

Adverse event analysis will include the percent of patients that experience events, the number of events, and the rate (represented as events per patient-year).

### 14.0 Detailed study timelines

The following assumptions are made with regards to the timelines for metrics including study initiation, site and subjects enrollment:

- The study will be initiated post approval of the HeartWare® VAS.
- As a follow-on “Expected number of subjects enrolled per month” is dependent upon scheduled visits in prior IDE trials to allow enrollment into this PAS.
- It is anticipated that “Expected duration of enrollment” will be within approximately 6 months of PMA approval.

Anticipated dates for key milestones and activities are listed below.

- |   |               |
|---|---------------|
| • Expected date of study initiation           | November 2012 |
| • Expected date of first IRB approval         | December 2012 |
| • Expected start of subject enrollment        | January 2013  |
| • Expected date of enrollment completion      | May 2013      |
| • Expected date of study follow-up completion | November 2017 |
| • Expected date for Final Report submission   | February 2018 |

## **15.0 Reporting Requirements (interim and final reports)**

Interim reports will be submitted at 6-months, 12 months, 18 and 24 months then yearly until the end of study follow-up. The report after the last patient has completed the 5 year (60 month) follow-up visit post original device implant will be the end of study, or final report.

## **16.0 Regulatory and Ethical Considerations**

This trial is to be conducted according to the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with ICH GCP and applicable regulatory requirement(s) including the Code of Federal Regulations 21CFR Part 812, 21CFR Part 54 and 21CFR Part 56.

Good Clinical Practice is a standard for the design, conduct, performance, monitoring, auditing, recording, analyses and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity and confidentiality of the trial subjects are protected.

The medical care given to, and medical decisions made on behalf of subjects should always be the responsibility of a qualified physician. Each individual involved in conducting the trial should be qualified by education, training and experience to perform his or her respective task(s).

### **16.1 IRB Approval**

All centers are required to obtain IRB approval of the Post Approval Study, addenda, and Informed Consent Forms (ICFs) prior to the study start at that center. This study will be undertaken only after full approval has been obtained from the applicable IRB and a copy of this approval has been received by HeartWare.

### **16.2 Informed Consent**

The patient must give written informed consent to participate prior to enrollment in the trial. No study procedures may be conducted unless consent is given and documented.

Prior to participation in the trial, the subject, should receive a copy of the signed and dated written ICF and any other pertinent written information.

All subjects will be informed that participation is voluntary and that they can cease participation at any time without necessarily giving a reason and without any penalty or loss of benefits to which they are entitled.

The signed and dated consent form will be kept by the Investigator.

### **16.3 Patient Data Protection**

Patients will be identified on the CRF by a patient identification number. The investigator will maintain a confidential patient identification list to link medical records and patient identification numbers.

All data used in analysis and reports will be used without identifiable reference to the patient. At all times throughout the study, confidentiality shall be observed by all parties involved.

All patients consented for this study will be informed and must agree to the use and disclosure of their study information by the institution and investigators to HeartWare, their agents and representatives, the FDA or other government agencies or review boards. This authorization is a HIPAA Authorization: Authorization to Use and Disclose Health Information. If the institution requires that an IRB-specific Confidentiality Authorization (HIPAA) form be used, then the site must provide a copy of this form to HeartWare for review and approval.

### **17.0 Investigators, Investigator Responsibility and Trial Administrative Structure**

The Investigator is responsible for ensuring that the clinical study is performed in accordance with the Post Approval Study protocol, Declaration of Helsinki, ICH GCP Guidelines, and Code of Federal Regulations 21CFR Part 812, 21CFR Part 54 and 21CFR Part 56 and any country laws, as applicable.

A Sub-Investigator (e.g., associates, residents, research fellows) is any individual member of the clinical trial team designated and supervised by the principal Investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions.

The Investigator must maintain a signed list of appropriately qualified persons to whom they have delegated significant trial-related duties which must be specified.

Trial-related medical decisions are the responsibility of a qualified physician (the Investigator or delegate).

The standard requirements for IRB review, informed consent, Patient data protection, investigator agreements, financial disclosures, protocol deviations, device accountability, and investigator reports will apply.

#### **17.1 Investigator Agreement**

Prior to study initiation, the Investigator must sign an Investigator Agreement (HeartWare or to provide Investigator Agreement template to sites). The Investigator Agreement identifies the Investigator's legal and ethical commitments with respect to the conduct of the clinical study as defined in 21 CFR Part 812, Part 56, Part 50, and Part 54.

## **17.2 Financial Disclosure**

A Financial Disclosure Form must be reviewed and signed by the Investigator and sub-investigator(s) prior to study initiation. HeartWare or designee will provide Financial Disclosure Form to sites. Updates to financial disclosure will be made during the course of the study and for 1 year following completion of the study (21 CFR Part 54). The Financial Disclosure form is required to record the Investigator's and Sub-Investigator's financial interests in HeartWare, which may be a potential source of bias in the outcome of the clinical study.

## **17.3 Post Approval Study Deviations and Medical Emergencies**

The Investigator will not deviate from the Post Approval Study protocol without the prior written approval of HeartWare except in medical emergencies or in unforeseen, isolated instances where minor changes are made that will not increase the subject's risk or affect the validity of the study. In addition HeartWare will not allow any deviations/waiver from the Inclusion and Exclusion Criteria.

In medical emergencies, prior written approval for deviations will not be required, but HeartWare personnel must be notified via telephone within 24 hours of occurrence.

If there are any circumstances during the clinical trial which can affect the safety of the subjects, users or third person, HeartWare and the investigator will take all necessary security measures immediately to protect the subjects, users and third persons against direct or indirect risk. HeartWare and the investigator have to inform the responsible IRB/IEC immediately about these new circumstances and the measures taken.

However in case of any deviation for a scheduled assessment e.g. out of window assessment, missing laboratory sample, and prior approval from HeartWare is required in advance for changes in or deviations from the Post Approval Study.

## **17.4 HeartWare (Sponsor)**

HeartWare accepts the responsibilities of the Sponsor.

## **17.5 Contract Research Organization**

A CRO (commercial, academic or other) may be employed by HeartWare to perform 1 or more of its trial-related duties and functions. The extent of the delegation must be specified in a contract between the involved parties. The CRO should implement quality assurance and quality control but HeartWare will have the right to supervise the implementation of the methods for quality assurance and quality control.



## **18.0 Documentation of Trial Data**

### **18.1 Case Report Forms**

An Electronic Data Capture (EDC) system will be utilized to collect all patient data during the course of the study. Data must be entered into eCRFs in English. The eCRFs are to be completed within 72 hours of the subject's visit, with the exception of results from tests performed outside the investigator's office, so that they always reflect the latest observations on the subjects participating in the study. A predetermined/designated individual (s) will be responsible for completion of the Electronic Case Report Forms (eCRFs). The PI will ultimately be responsible for the review, completion and accuracy of data entered into the eCRF.

Completed eCRFs will be verified by a Sponsor monitor at the site at regular intervals throughout the study. The Investigator will allow the monitor and the FDA or other regulatory bodies to review the study files, patient CRFs, medical records and other study-related documents.

### **18.2 Data Management**

#### **18.2.1 eCRF**

During data entry in the eCRF, queries will be directly issued to clarify missing data, inconsistencies and incorrect values. After completion of the eCRF, further queries will be issued to the Investigator to clarify (e.g., inconsistencies resulting out of the medical and manual review). Resolutions of queries will be made by the Investigator or the trial site's designated persons.

#### **18.2.2 Coding**

Medication names will be coded using the World Health Organization Drug Dictionary. Adverse events will be coded according to the NIH funded INTERMACS® registry definitions. Adverse events categorized as "Other" within the INTERMACS® definitions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

#### **18.2.3 Source data**

Source data is all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents which comprise clinical documentation, data and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments and data and records arising from other departments such as the pharmacy, laboratory and medico-technical departments).

Clinical documentation relevant to the trial includes all records in any form including, but not limited to:

- Medical history/physical condition of the patient before enrollment sufficient to verify
- Post Approval Study entry criteria
- Dated and signed notes for specific results of procedures and exams
- Laboratory reports
- Information related to adverse events
- Notes on subject's condition with device implanted and when explanted
- Stroke Scale and Quality of Life studies
- Discharge Summaries/Procedure reports
- Autopsy reports

All clinical documentation and data arising from the trial are to be kept by the Investigator who has to provide direct access for trial-related monitoring, audits, IEC review, and regulatory inspection.

At the end of the trial, the Investigator will receive a certified copy of all data captured for their subjects, in human readable form, on a read-only CD-ROM. Data captured of all subjects will be sent to the sponsor in human readable form, on a read-only CD-ROM for archiving.

#### **18.2.4 Data Review and Data Quality Assurance**

All eCRFs will be reviewed for completeness and clarity. Missing data will be investigated by the monitor and clarified by study personnel as necessary. HeartWare may request additional documentation such as physician procedure notes or written summaries relating to adverse events or procedures. HeartWare will be responsible for the quality control of the database and confirming the overall integrity of the data.

## **19.0 Data Monitoring and Administrative Requirements**

### **19.1 Monitoring of the Study**

HeartWare or designees will perform on-site monitoring visits as frequently as necessary. Visits are usually made at regular intervals. At these visits the monitor will compare the data entered into the eCRFs with the hospital or clinic records (source documents). At a minimum, source documentation must be available to substantiate proper ICF procedures, adherence to protocol procedures, adequate reporting and follow-up of AEs, administration of concomitant medication and device receipt/ return records.

The sponsor expects that, during monitoring visits, the investigator (and as appropriate the study coordinator) will be available, the source documentation will be available, and a suitable environment will be provided for review of study-related documents.

### **19.2 Quality System, Audit and inspection**

HeartWare is responsible for implementing and maintaining quality assurance and quality control systems with written Standard Operating Procedures. HeartWare is responsible for ensuring that all parties involved with the trial agree to direct access to all trial-related sites, source data and documents, and reports for the purposes of monitoring and auditing by HeartWare, and inspection by FDA.

### **19.3 Audit**

The Investigator will permit an appointed person by the Quality Assurance Unit of HeartWare to audit the facilities and documentation at agreed times. Auditors are independent of the clinical trial and its performance.

An audit is the systematic and independent examination of trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data recorded, analyzed and accurately reported according to the Post Approval Study protocol, HeartWare Standard Operating Procedures, GCP and applicable regulatory requirements.

### **19.4 Inspection**

Inspection is the act by the FDA of conducting an official review of the documents, facilities, records and other resources that are deemed by the FDA to be related to the clinical trial and that may be located at the trial site, at HeartWare, at the CRO, or at other facilities deemed appropriate by the regulatory authorities. The Investigator is obliged to cooperate with any inspection.

In the event of an FDA audit, the Investigator must allow FDA access to the study records for inspection and copying. The Investigator must inform HeartWare of any FDA audit and provide HeartWare with a copy of Form FDA 483 (List of Observations), if issued.

## 19.5 Maintenance of Study Documentation

The Investigator must maintain the following documents throughout the study:

- Post Approval Study Protocol
- IRB Approvals and Correspondence
- IRB Approved ICF
- Correspondence with HeartWare
- Electronic Signature Authorization Form
- Device Accountability (if applicable)
- Investigator Agreements
- Curriculum Vitae
- Financial Disclosure Forms
- Telephone Logs
- eCRFs
- Monitoring Visit Log
- Laboratory Accreditation and Normal Values
- Site Delegation and Responsibility log
- Source Documents supporting information on eCRFs
- Any other study specific documents

## 19.6 Protocol Modifications

Changes to the protocol during the trial will be documented as amendments. The amended protocol will be signed by the relevant personnel at HeartWare, and by the Investigator(s).

Depending on the contents of the amendment and local legal requirements, the amendment will be submitted to the relevant IRB.

If an amendment substantially alters the trial design, increases the potential risk to the patients or affects the treatment of the patient, then the Informed Consent form must be revised and submitted to the relevant IRB/IEC for review and approval. When a patient is currently undergoing trial procedures and is affected by the amendment, then the patient must be asked to consent again using the new Informed Consent form. Informed Consent form must be used to obtain consent from new subjects before enrollment.

## 19.7 Compliance and Investigational Site Termination

### 19.7.1 Compliance

Compliance is the adherence to all trial-related requirements, to Good Clinical Practice (GCP) and to regulatory rules and regulations.

### **19.7.2 Investigational Site Termination**

An initiative for center closure or study termination can be taken at any time either by the sponsor or by the investigator, provided there is reasonable cause and sufficient notice is given in advance of the intended termination. HeartWare reserves the right to terminate an investigational site from the study for any of the following reasons:

- Repeated failure to complete case report forms
- Failure to obtain ICF
- Failure to report SAEs and UADEs
- Repeated protocol violations
- Failure of investigator to comply with training or Instructions for Use
- Insufficient patient and caregiver/Companion training

### **19.8 Record Retention**

HeartWare and all participating Investigators must establish and maintain records and reports. The Investigator must maintain the signed Informed Consent Forms, eCRFs, study documentation (listed above) and source documents for at least 4 years after study completion or termination. In accordance with the Investigator Agreement, HeartWare should be contacted if the Principal Investigator plans to leave or otherwise absent themselves from the investigational site.

### **19.9 Site Training**

Sites will be trained by HeartWare on the device usage and on implant technique as appropriate. Training on GCP, Clinical Protocol required procedures and data collection will be provided by HeartWare and its vendor(s).

### **19.10 Confidentiality of trial results**

The results of this trial are confidential and are not to be transmitted to a third party in any form or fashion. All persons involved in the trial are bound by this confidentiality clause.

### **19.11 Publication policy**

The results of the trial will be published as soon as the data for the primary endpoint is available, initially as a poster/presentation at a congress, and then as a full publication in an international heart failure or cardiothoracic surgical journal. Draft manuscripts of publications will be prepared in co-operation between HeartWare and the Coordinating Investigator/Investigator(s). Joint publications are only possible if all parties agree. All editorial decisions will be made jointly by HeartWare and the Coordinating Investigator/Investigator(s).

HeartWare reserves the right to review any publication pertaining to the trial before it is submitted for publication. Neither party has the right to prohibit publication unless publication can be shown to affect possible patent rights or regulatory submission requirements. In case of discrepancies with other contracts, the provisions of the protocol shall prevail.

### **19.12 Final report**

A final report, integrating medical and statistical aspects, will be prepared. This will be authorized by the relevant personnel of HeartWare, and the Coordinating Investigator on behalf of the Investigators. The Investigator(s) will be provided with a copy of the summary of the final report. HeartWare will provide the FDA and IRB/IEC with the complete clinical trial report within 1 year after the end of the trial or on request, where required.

[REDACTED]		
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]

[REDACTED]		
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]



[illegible]

\_\_\_\_\_

\_\_\_\_\_

██████████

██████████

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]



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[REDACTED]	
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	

- [REDACTED]  
[REDACTED]
- [REDACTED]
- [REDACTED]  
[REDACTED]
- [REDACTED]
- [REDACTED]  
[REDACTED]

[REDACTED] [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

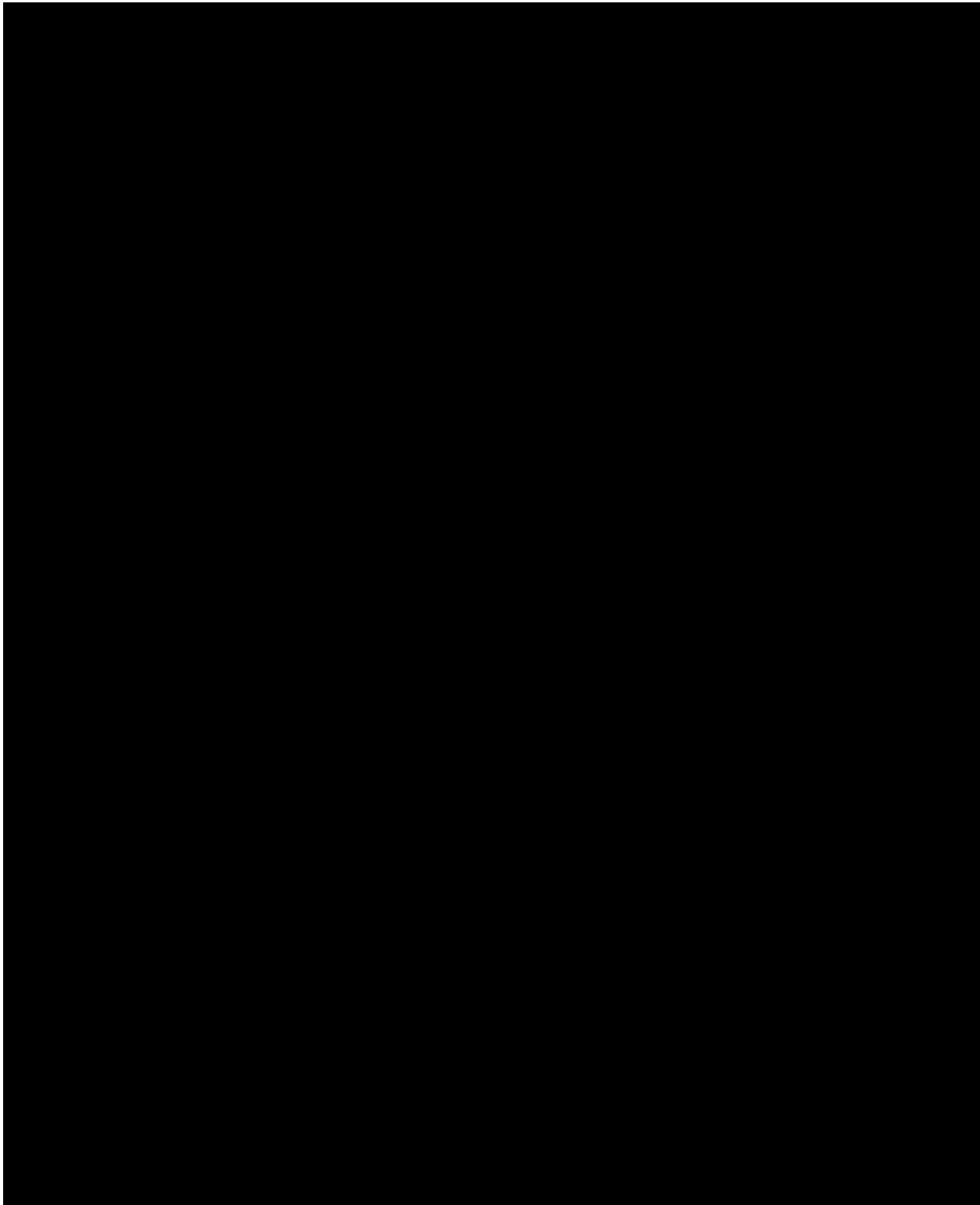
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[REDACTED]

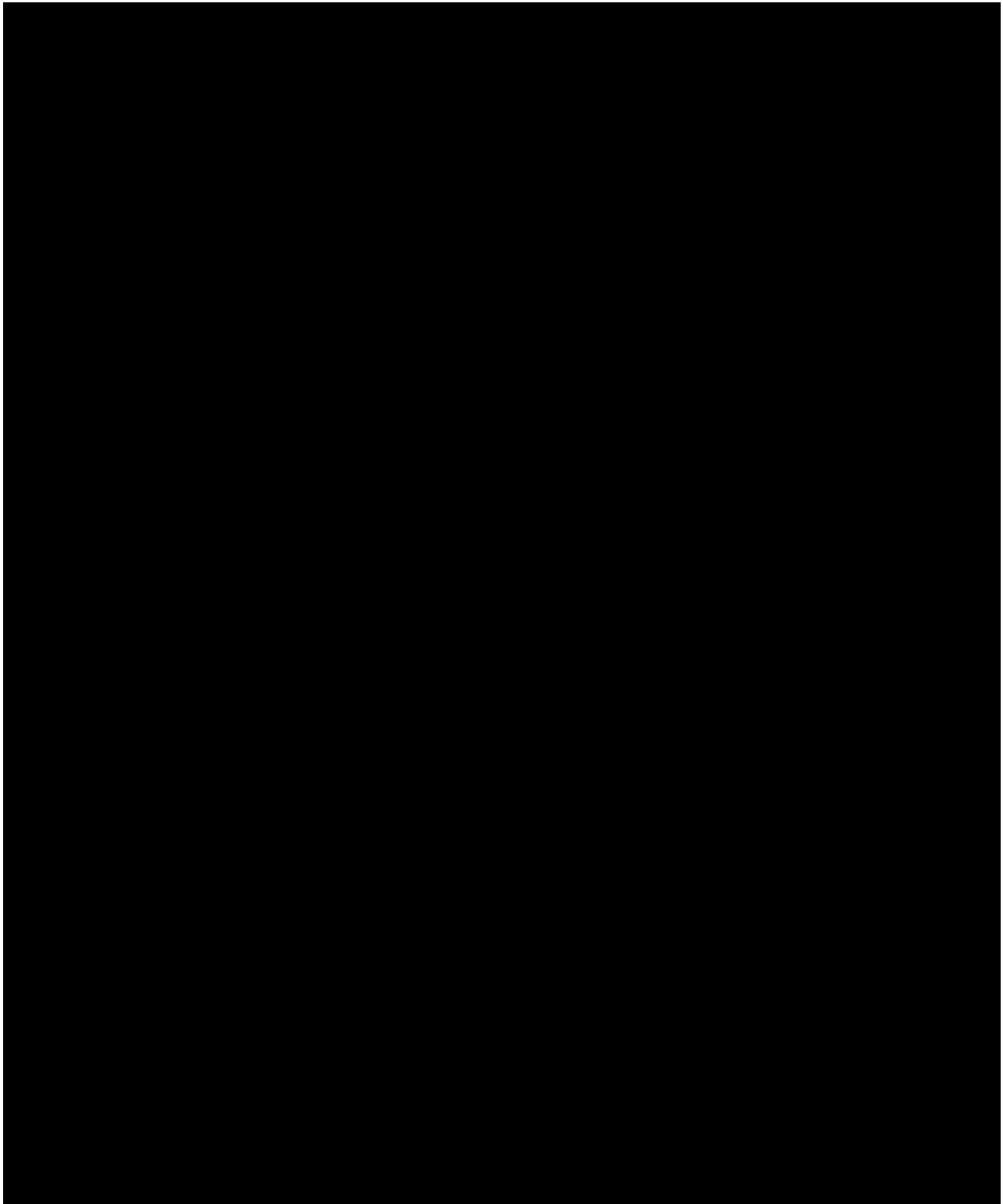
[REDACTED]

[REDACTED]

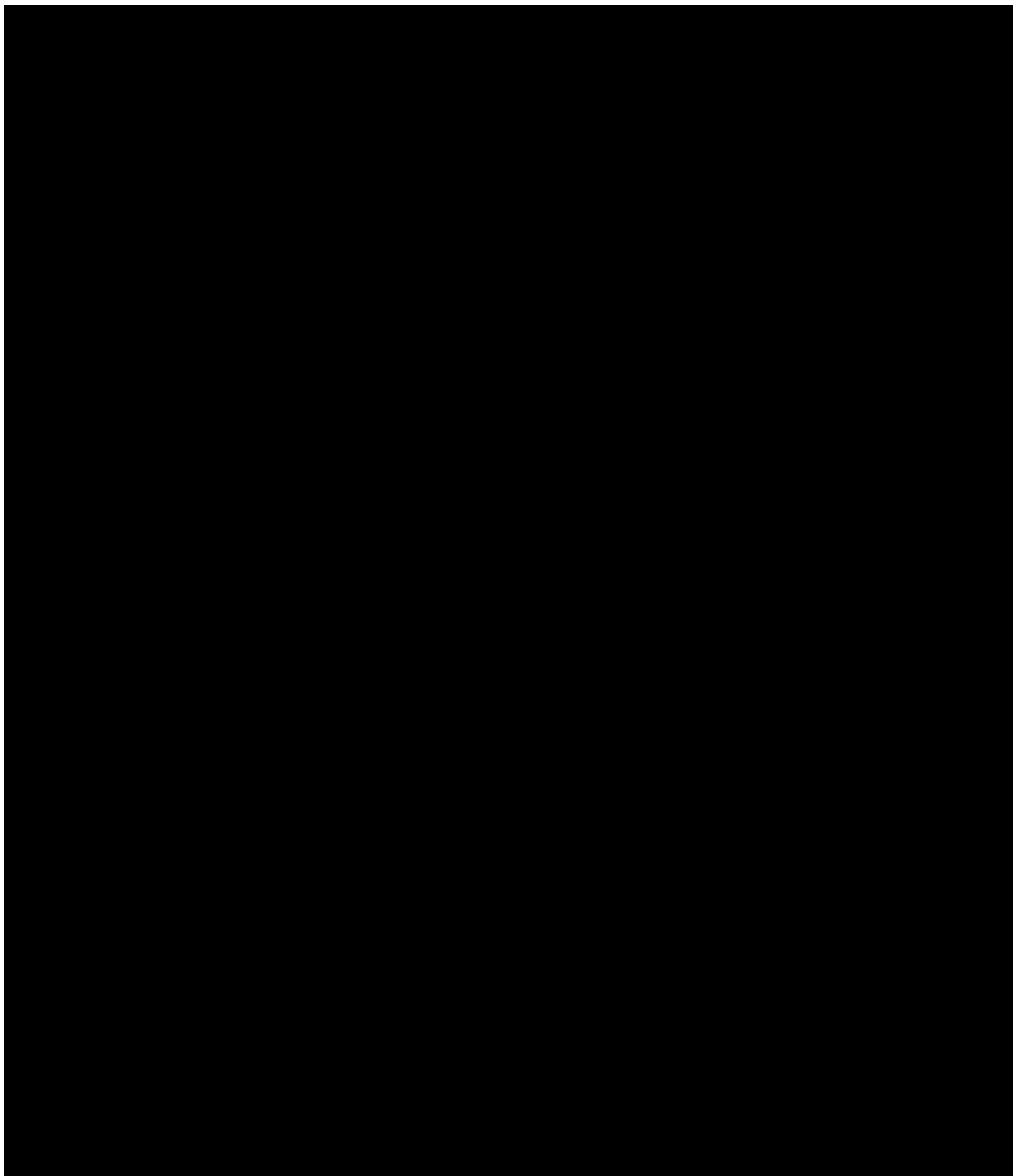
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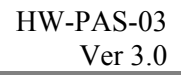


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[illegible]



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[REDACTED]

[REDACTED]

[REDACTED]

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[REDACTED]

[REDACTED]

[REDACTED]



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